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EXAMINER	
POPA, ILEANA	

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1633	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

efspatents@sbiplaw.com

Office Action Summary	Application No.	Applicant(s)	
	10/652,814	UNGER, GRETCHEN M.	
	Examiner	**Art Unit**	
	ILEANA POPA	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 December 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *66,67,87-94,133-137 and 139-141* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application

6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 66-95,97-100,102-109,111-116,118,119,122-127,133-137 and 139-141.
Continuation of Disposition of Claims: Claims withdrawn from consideration are 68-86,95,97-100,102-109,111-116,118,119,122-124,126 and 127.

DETAILED ACTION

1. Claims 1-65, 96,101,110, 117, 120, 121, 125, 128-132, and 138 have been cancelled. Claims 68-86, 95, 97-100, 102-109, 111-116, 118, 119, 122-124, 126, and 127 have been withdrawn. Claims 66, 88, 89, 94, and 139 have been amended.

Claims 66, 67, 87-94, 133-137, and 139-141 are under examination.

2. All rejections pertaining to claim 138 are moot because the applicant cancelled the claim in the reply filed on 12/22/2010.

The provisional rejection of claims 67, 87, 88, 90, 94, 133, 134, 136, 137, and 139-141 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 8 and 11 of copending Application No. 12/027,863 is moot because Application No. 12/027,863 has been abandoned.

The rejection of claims 66, 67, 87-94, 133-137, and 139-141 under 35 U.S.C. 112, second paragraph, as being indefinite is withdrawn in response to the amendment field on 12/22/2010.

Upon further considerations, the following rejections are withdrawn in favor of new rejections using a new reference which provides a better motivation to arrive at the claimed invention:

The rejection of claims 66, 67, 87-89, 91-93, 135, 137, and 139 under 35 U.S.C. 103(a) as being unpatentable over Iwata et al. (J. Microencapsulation, 1992, 9: 201-214) in view of each Davies et al. (Journal of Colloid and Interface Science, 1987, 116:

88-99, Abstract), Levy et al. (WO 96/20698), Chang et al. (Journal of Pharmaceutical Sciences, 1996, 85: 13225-1330), and Kondo et al. (Anal Biochem, 1991, 198: 3035, Abstract); and

The rejection of claims 66, 67, 87-89, 91-94, 133-135, 137, and 139-141 under 35 U.S.C. 103(a) as being unpatentable over Iwata et al. taken with each Davies et al., Levy et al., Chang et al., and Kondo et al., in further view of Schneider et al. (FEBS Letters, 1998, 429: 269-273).

Specification

3. The disclosure remains objected to for the use of the trademarks Qiaquik, Zymoclean, Synergel, SybrGold, and Storm 860 (p. 23, lines 20-25). The trademarks should be capitalized wherever they appears.

It is noted that the amendment filed on 12/22/2010 is not sufficient to overcome the instant objection because the trademaks Qiaquik, Zymoclean, and Synergel have not been capitalized.

Double Patenting

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In*

re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 66, 67, 87, 88, 90, 94, 133, 134, and 136-141 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 25-28 of copending Application No. 11/622,359. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are obvious variants.

The instant claims are drawn to a composition of nanocapsules comprising (i) a surfactant micelle consisting of a bioactive component that has a therapeutic effect and a surfactant having an HLB value of less than about 6.0, and (ii) a shell surrounding the surfactant micelle, wherein the shell comprises a precipitate containing a polypeptide and Li^+ and wherein the polypeptide provides specific cellular by binding to cell surface antigens or receptors; the particles have an average diameter of less than 50 nm as measured by atomic force microscopy after drying of the particles (claims 66 and 139). The polypeptide comprises tenascin (claims 133, 134, 140, and 141), the bioactive component is a polynucleotide (claims 67 and 139), which can be associated with a nucleic acid condensing agent (claim 137), the surfactant has a HLB of less than 5.0

(claim 88) and can be non-ionic (claim 87) or is selected from the group recited in claims 90 and 136. The specification defines that the polynucleotide could be an anti-sense DNA (p. 23, line 1).

The application claims drawn a collection of particles having a bioactive component, a surfactant with an HLB less than 6.0, a biocompatible polymer, and a cell recognition component having affinity for a cell receptor; the average diameter of the particles is less than 50 nm as measured by atomic force microscopy after drying of the particles (claim 25), wherein the bioactive component is a polynucleic acid (claim 28) and wherein the biocompatible polymer is tenascin claims 26 and 27). The specification defines that: **(i)** the surfactant can be a non-ionic surfactant or 2,4,7,9-tetramethyl-5-decyn-4,7-diol (i.e., a surfactant that has an HLB of less than 5.0, as recited in the instant claims 87, 88, 90, and 136), **(ii)** the particles comprise surfactant micelles containing surfactant and a bioactive agent, **(iii)** the biocompatible polymer forms a shell surrounding the surfactant micelles, and **(iv)** the biocompatible polymer is precipitated by cations such as Li^+ (p. 9. lines 21-23. p. 10, lines 1-21, p. 75, lines 15-18, p. 76, lines 3-13). With respect to the limitation of nanocapsule, the specification disclosed that the particles can be formulated as nanocapsules (p. 11, lines 6 and 7). With respect to the limitation of the polynucleotide being associated with a nucleic acid condensing agent, this is not innovative over the prior art, which teaches that condensing agents are always used when delivering nucleic acids via nanoparticles.

Thus, the application claims and the instant claims are obvious variants of one another.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The applicant has requested that the obvious-type double patenting rejection set forth by the examiner be held in abeyance. The applicant's comments are acknowledged, however the rejection will be maintained until a terminal disclaimer is filed or claims are amended to obviate the rejection

6. Claims 66, 67, 87, 88, 90, 93, 94, 133, 134, 136, 137, and 139-141 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 29, 31, 33, 37, and 42 of U.S. Patent No. 6,632,671.

The instant claims are drawn to a composition of nanocapsules comprising (i) a surfactant micelle consisting of a bioactive component that has a therapeutic effect and a surfactant having an HLB value of less than about 6.0, and (ii) a shell surrounding the surfactant micelle, wherein the shell comprises a precipitate containing a polypeptide and Li^+ and wherein the polypeptide provides specific cellular by binding to cell surface antigens or receptors; the particles have an average diameter of less than 50 nm as measured by atomic force microscopy after drying of the particles (claims 66 and 139). The polypeptide comprises tenascin (claims 133, 134, 140, and 141), the bioactive component is a polynucleotide (claims 67 and 139), which can be associated with a nucleic acid condensing agent (claim 137), the surfactant has a HLB of less than 5.0 (claim 88) and can be non-ionic (claim 87) or is selected from the group recited in

claims 90 and 136. The specification defines that the polynucleotide could be an anti-sense DNA (p. 23, line 1).

The patent claims recite a plurality of particles comprising a surfactant with an HLB less than 5.0, a bioactive hydrophobic component (i.e., a bioactive component), and a biocompatible polymer, wherein the particles have an average diameter of less than 50 nm as determined by atomic force microscopy and wherein the biocompatible polymer is precipitated in the presence of a cation (claims 29, 37, and 42). The surfactant can be a non-ionic surfactant or 2,4,7,9-tetramethyl-5-decyn-4,7-diol (claim 33), as recited in the instant claims 87, 90, and 136, and the particles further comprise a water-miscible solvent (claim 31). With respect to the limitation of the biocompatible polymer providing specific cellular uptake, the specification discloses that the biocompatible polymer can be tenascin (see fig. 7B, and also column 3, lines 6-8). The specification discloses that the biocompatible polymer forms a shell surrounding the surfactant micelles containing the bioactive component and the surfactant, the hydrophobic bioactive component can be a polynucleic acid, and that the precipitating cation is Li^+ (Abstract, column 3, lines 25-32, column 5, lines 37-59, column 7, lines 32-37, column 9, lines 40-45, column 10, lines 42-66, column 15, lines 30-32). With respect to the limitation of HLB being less than 6.0, the patent claims recite an HLB less than 5.0 that anticipates the claimed HLB of less than 6.0. With respect to the limitation of nanocapsules, the specification discloses that the particles are formulated as nanocapsules (Abstract). With respect to the limitation of the polynucleotide being associated with a nucleic acid condensing agent, this is not innovative over the prior art,

which teaches that condensing are always used when delivering nucleic acids via nanoparticles.

Therefore, the patent claims and the instant claims are obvious variants of one another.

The applicant has requested that the obvious-type double patenting rejection set forth by the examiner be held in abeyance. The applicant's comments are acknowledged, however the rejection will be maintained until a terminal disclaimer is filed or claims are amended to obviate the rejection

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 66, 67, 87-89, 93, 135, 137, and 139 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ueda et al. (J. Microencapsulation, 1997, 14: 593-605), in view of each Landry et al. (Biomaterials, 1996, 17: 715-723), Ghitescu et al. (J. Cell Biol., 1986, 102: 1304-1311), Kondo et al. (Anal Biochem, 1991, 198: 3035, Abstract, of record), and Boulikas (U.S. Patent No. 6,030,956).

Ueda et al. teach nanoparticles comprising: **(i)** a core provided by loperamide (i.e., a bioactive compound having a therapeutic effect) and a surfactant micelle, wherein the surfactant has a HLB less than 5.0; and **(ii)** a surrounding PVA-coated biodegradable polymer shell; the surfactant with a HLB less than 5.0 is Span (i.e., non-ionic and having a critical micelle concentration of less than 200 μM). The nanoparticles further comprise a water-miscible solvent (claims 66, 87-89, 93, 135, and 139) (Abstract; paragraph bridging p. 594 and 595; p. 599, second full paragraph; p. 600, Table 4).

Ueda et al. do not teach a shell comprising a polypeptide (claims 66 and 139). Landry et al. teach that nanoparticles formed by the solvent-evaporation technique (such as the one of Ueda et al.) require either PVA or albumin for their production (p. 715, column 2, second full paragraph). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Ueda et al. by replacing PVA with albumin to achieve the predictable result of obtaining drug-loaded nanoparticles. It is noted that, by doing such, one of skill in the art would have obtained a nanoparticle having a shell comprising albumin which provides specific cellular uptake by binding to a cell-surface receptor (see Ghitescu et al., Abstract).

Ueda et al. and Landry et al. do not teach precipitating the albumin coat with a cationic precipitating agent such as Li^+ (claims 66 and 139). However, doing such is suggested by the prior art. For example, Ueda et al. teach that a precipitated shell enhances drug entrapment within the nanoparticles (p. 598). Furthermore, using Li^+ to precipitate proteins was routine in the prior art (see Kondo et al., Abstract). It would

have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Ueda et al. and Landry et al. by further precipitating the protein coat with Li^+, with a reasonable expectation of success. One of skill in the art would have been motivated to do so in order to increase drug entrapment within the nanoparticles. One of skill in the art would have reasonably expected to be successful in doing such because the prior art teaches that Li^+ can be successfully used to precipitate proteins.

Ueda et al., Landry et al., and Kondo et al. do not teach a particle size of 50 nm (claims 66 and 139). However, they do teach that particle size can optimized by varying parameters such as the homogenization conditions, PLA and albumin concentration, or PLA and albumin molecular weight (see Ueda et al., p. 595 and 597; Landry et al., p. 716, column 2, first and second full paragraphs). Furthermore, the prior art teaches the necessity of avoiding the degradation of bioactive agents within lysosomes by using particles of about 50-60 nm which could be internalized via caveolae (see Boulikas, column 12, lines 45-54, column 16, lines 38-49). It would have been obvious to one of skill in the art, at the time the invention was made, to vary the parameters in the method of optimize the size of the nanoparticles of Ueda et al., Landry et al., and Kondo et al. with the purpose of obtaining particles suitable of being delivered inside the cells via caveolae.

With respect to the limitation of the bioactive agent being a polynucleotide (claim 67), it would have been obvious to one of skill in the art to use the particles taught by the combined teachings above in gene therapy, because the prior art teaches the

necessity to use gene therapy to treat diseases such as cancer (see Boulikas, Abstract, column 7, line 50 through column 8, line 16, column 10, line 66 and 67). With respect to the limitation of a condensing agent (claim 137), Boulikas teaches using DNA condensing agents such as histones to increase the nuclear import of the polynucleic acid to be expressed within the cell (column 12, lines 45-54). It would have been obvious to one of skill in the art, at the time the invention was made, to further include a histone, with a reasonable expectation of success. One of skill in the art would have been motivated to do so in order to increase the expression rate of the therapeutic nucleic acid. One of skill in the art would have reasonably expected to be successful in doing such because the prior art teaches the successful use of condensing agents such as histones to deliver nucleic acids to the nucleus.

Thus, the claimed invention was *prima facie* obvious at the time it was made.

The applicant argues that, although Ueda describes varying the nanoparticle size, the description is more inclined to motivate the ordinarily skilled artisan to increase the nanoparticle size, rather than decrease it. Ueda states that particle size decreases with increasing PVA concentrations, but that lower concentrations of PVA are optimal (page 597, second half of first paragraph under Results and Discussion section). Table 1 on page 598 shows that even at the highest concentration of PVA listed (2.0% w/v), the particles produced still have a mean diameter of 173.9 nm. The applicant argues that, when describing the effects of the manufacturing conditions and formulation on the size of the nanoparticles, Ueda notes that an increase in number of homogenizer cycles

after 3-5 cycles does not result in a significant difference in particle size (page 597, first half of first paragraph under Results and Discussion section). Thus, the ordinarily skilled artisan would not be likely to believe that running additional homogenization cycles would lead to a decrease in particle size beyond 164 nm. Finally, Ueda discusses the inclusion of hydrophobic surfactants to the W/O/W formulation noting that the nanoparticle size consequently either increased (for sorbitan monostearate) or remained the same (for sorbitan trioleate) across a range of surfactant concentrations (pages 601 and 602). Furthermore, sorbitan monostearate, which is associated in Ueda with increasing nanoparticle size, is indicated as the most efficient surfactant (page 601, paragraph directly below Figure 3 Legend), followed by a statement that increasing sorbitan monostearate concentrations results in larger nanoparticles (page 601, second-to-last paragraph). Ueda makes no explicit statement regarding desirability of changing the size of the nanoparticles obtained through the process described therein, but those disclosures the reference does include would be likely to teach the ordinarily skilled artisan away from using hydrophobic surfactants to decrease particle size, let alone to achieve nanoparticles having an average diameter of less than 50 nm.

The argument that Ueda would motivate the ordinarily skilled artisan to increase the nanoparticle size, rather than decrease it is not found persuasive because it is just an argument not supported by any evidence. There is no teaching in Ueda that particles with smaller sizes are not desirable. The citations indicated by the applicant only state which conditions result in larger particle size and which conditions result in smaller particle size. According to the applicant, Ueda teaches that an increase in

number of homogenizer cycles after 3-5 cycles does not result in a significant difference in particle size. This statement is incomplete, as Ueda teaches that other variable influence the particle size (see p. 597). Thus, one of skill in the art would know what parameters to vary such as to decrease the particle size. Furthermore, an obviousness-type rejection is based on the knowledge available in the prior art as a whole. Landry also teaches what parameters influence the size of the particles. Importantly, Landry teaches obtaining nanoparticles of 100 nm (i.e., below 164 nm). Bazile et al. (Biomaterials, 1992, 13: 1093-1102) teach that albumin-coated nanoparticles, such as the ones taught by the combination of art cited above, can be obtained in different sizes, including 50 nm (Abstract; p. 1094, column 1, second full paragraph; p. 1097, column 1). Thus, one of skill in the art would have known how to decrease the particle size to 50 nm. Apart from an argument, the applicant did not provide any evidence that one of skill in the art would not have been successful in further reducing the size of the particles by varying the parameters taught by the prior art as being important to obtain particles with desired sizes.

The applicant argues that, by reading Landry, one of skill in the art would not have had any inclination to change the nanoparticle size. This argument is not found persuasive because it is directed individually to Landry. The instant rejection is based on a combination of references and it is this combination which provides the motivation to change the nanoparticle size. For the same reason, the argument that Kondo does not mention particles is not found persuasive, as Kondo does not have to teach each

and every claim limitation.

The applicant argues that Boulikas' discussion of caveolae-mediated entry into cells is specific to his liposomal delivery vehicle, in contrast with the polymeric particles of Ueda and Landry. Thus, a reading of Boulikas does not leave the person of ordinary skill in the art inclined to apply these teachings to Ueda and/or Landry, let alone to decrease the particle size to less than 50 nm.

This is not found persuasive. The teaching in Boulikas is related to the size of particle suitable to deliver agents inside cells, regardless of the nature of the particles. Importantly, prior art other than Boulikas teaches the necessity to use particles smaller than 80 nm (such as 20-30 nm nanoparticles) for efficient delivery to cells (see Wolfert et al., Gene Therapy, 1996, 3: 269-273, of record; p. 270, column 1, p. 271, column 1. p. 272, column 2, firs full paragraph). Based on the teachings in the art as a whole, one of skill in the art would have known and be motivated to use nanoparticles smaller than 50 nm.

The applicant argues that Boulikas provides no data indicating an end-product with a diameter of less than 50 nm. It was known, at the time of the instant invention, that the manufacture of a liposome (such as Boulikas's liposomes) of less than 100 nanometers was difficult to achieve due to their intrinsic instability.

This argument is not material to the instant rejection, which is not based on using liposmes.

The applicant argues that, in making the instant rejection, the examiner has used impermissible hindsight. The applicant argues that Ueda, and/or any of the other references, fails to teach the shell comprising a polypeptide and Li^+. The applicant argues that Kondo teaches the use of lithium chloride and ethidium bromide to separate DNA from protein (and RNA). Precipitation (separation) of RNA and proteins from DNA preparations would not be equated with the instant application's including Li^+ in the shell surrounding the instantly disclosed surfactant micelle. The person of ordinary skill in the art would not be prompted to combine the teachings of Kondo with those of Ueda and Landry.

This is not found persuasive. Ueda teaches the necessity to precipitate the shell of their nanoparticles to enhance drug entrapment within the nanoparticles. Ueda does not teach precipitating with Li^+ or any other cation because they do not teach a protein shell. However, the combination of the cited art teaches a nanoparticle with a protein shell. The prior art teaches that protein shells in nanoparticles could be precipitated with cations such as Ca^{2+}, Ba^{2+}, Gd^{2+}, Ni^{2+}, $Al^{2+}$and Mn^{2+} (see Magdassi et al., WO 98/07410, Abstract; p. 9, lines 25-29; claims 4 and 6). Kondo teaches that Li^+ is also a protein-precipitating agent. One of skill in the art would have known that any protein-precipitating agent, including the cations taught by the prior art, would work. Apart from an argument, the applicant did not provide any evidence to the contrary.

The applicant argues that, at the time the instant invention was made, there had been, for at least ten years, a need in the field of drug delivery to combine cell-targeting and efficient, non-degradative uptake. The emerging view was that any solution was likely to be more complex than originally believed (i.e., unpredictable, with no reasonable expectation of success). Applicant's nanocapsule system addresses this long-felt need, producing cell-targeted, stabilized nanocapsules of sub-50 nm size that avoid substantial lysosomal accumulation and degradation, providing uniform, intact delivery of a therapeutic agent. Heidel et al. summarized the views held by many for years, i.e., that addressing the challenges of drug delivery isn't simply a matter of identifying useful ingredients or adding components to known vesicle structures. Accordingly, it is submitted that the claimed nanocapsules meet significant, long- felt needs and are a significant leap over the teachings of the prior art.

This is not found persuasive. Establishing a long-felt need requires evidence that an art recognized problem existed in the art for a long time without a solution (see MPEP 716.04 [R-2]); however, there is no such evidence. As indicated above, albumin-coated nanoparticles with sizes of 50 nm or smaller were routinely used in the prior art for efficient and non-degradative uptake. Attaching targeting ligands to albumin-coated nanoparticles for specific delivery to cells of interest was also routine in the prior art (see Sheng et al., Yao Xue Xue Bao, 95, 30: 706-710, Abstract). Therefore, at the time the invention was made, the prior art offered a solution to the problem of targeted and non-degradative drug delivery and the argument of long-felt need is not found persuasive. The argument that Heidel et al. indicate that targeted drug delivery isn't simply a matter

of identifying useful ingredients or adding components to known structures is not found persuasive. The proposed modifications are replacing PVA with albumin to obtain albumin-coated nanoparticles and attaching targeting ligands to the albumin coat. The prior art teaches successfully replacing PVA with albumin to obtain albumin-coated nanoparticles and successfully attaching targeting ligands to the albumin coat. Thus, one of skill in the art would have certainly expected to be successful in combining the teachings in the prior art to arrive at the claimed invention. Apart from an argument, the applicant did not provide any evidence to the contrary.

9. Claims 66, 67, 87-90, 93, 135-137, and 139 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ueda et al. taken with each Landry et al., Ghitescu et al., Kondo et al., and Boulikas, in further view of Krishnan et al. (Colloids Surfaces A: Physicochem. Eng. Aspects, 1999, 149: 355-366).

The teachings of Ueda et al., Landry et al., Ghitescu et al., Kondo et al., and Boulikas are applied as above for claims 66, 67, 87-89, 93, 135, 137, and 139. Ueda et al., Landry et al., Ghitescu et al., Kondo et al., and Boulikas do not teach acetylenic diols such as 2, 4, 7, 9-tetramethyl-5-decyne-4,7-diol (claims 90 and 136). However, using such is suggested by the prior art. For example, Ueda et al. teach that using surfactants with an HLB less than 5.0 is necessary for efficient incorporation of therapeutic agents (see p. 599). Furthermore, 2, 4, 7, 9-tetramethyl-5-decyne-4,7-diol was known in the prior art as having an HLB of 3 (see Krishnan et al., Abstract, p. 357, column 2, last paragraph). It would have been obvious to one of skill in the art, at the

time the invention was made, to modify the nanoparticles of Ueda et al., Landry et al., Ghitescu et al., Kondo et al., and Boulikas by replacing their surfactant with any surfactant with an HLB lower than 5.0, including the well-known 2, 4, 7, 9-tetramethyl-5-decyne-4,7-diol, to achieve the predictable result of efficiently incorporating hydrophilic therapeutic agents such as nucleic acids into nanoparticles.

Thus, the claimed invention was *prima facie* obvious at the time it was made.

The applicant argues that Ueda teaches that the use of hydrophobic surfactants can increase nanoparticle size, and certainly won't decrease it.

In response, the applicant has no basis in and cannot simply assume from Ueda's teachings that the use of hydrophobic surfactants, in general. increases the size. All that Ueda teaches is that increasing the amount of sorbitan monostearate (which has an HLB of 4.7) results in larger nanoparticles; this does not mean that sorbitan monostearate is not suitable to obtain small nanoparticles if used at lower concentrations; furthermore, Ueda teaches that increasing the concentration of sorbitan trioleate (which has an HLB of 1.8) does not result in increased particle size (see Fig. 4). It is noted that the prior art teaches what parameters to vary in order to obtain small nanoparticles.

The applicant argues that Krishnan is an entirely unrelated field from that of the instant invention, as well as from that of the other references cited.

This is not found persuasive because Krishnan was used to evidence that 2, 4, 7, 9-tetramethyl-5-decyne-4, 7-diol (low HLB) was well-known in the prior art. Based on Ueda's teachings that surfactants with very low HLBs are suitable to form nanoparticles, one of skill in the art would have known and would have reasonably expected to be successful in using any low HLB surfactant taught by the prior art. For the same reasons, the argument that one of skill in the art would be inclined to use the Surfynol 440 surfactant, rather than the Surfynol 104H is not found persuasive. The instant rejection is based on forming albumin-coated nanoparticles and not on interaction between surfactants and maleic anhydride copolymers. The cited prior art teaches to use surfactants with low and not high HLB to obtain small albumin coated nanoparticles. One of skill in the art would have had no reason to select a surfactant with a high HLB.

The applicant argues that Krishnan fails to cure the defects of the combination of the references discussed above. This is not found persuasive because there is no defect to be cured.

New Rejections

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 66, 67, 87-89, 91-93, 135, 137 and 139 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matsuzawa et al. (Biol Pharm Bull, 1995, 18: 1718-1723), in view of each Davies et al. (Journal of Colloid and Interface Science, 1987, 116: 88-99, Abstract, of record), Levy et al. (WO 96/20698, of record), Chang et al. (Journal of Pharmaceutical Sciences, 1996, 85: 1325-1330, of record), and Kondo et al. (Anal Biochem, 1991, 198: 3035, Abstract, of record).

Matsuzawa et al. teach nanoparticles comprising: **(i)** a surfactant micelle comprising core provided by insulin (i.e., a bioactive component having a therapeutic effect), wherein the surfactant is Span 80, i.e., a nonionic surfactant having an HLB of 4.3 (see Davies et al., Abstract) and a critical micelle concentration of less than 200 μM; and **(ii)** a surrounding shell comprising gelatin (i.e., a polypeptide); the microparticles further comprise Tween 80, biocompatible oils, and a water-miscible solvent (claims 66, 87-89, 91-93, and 135) (Abstract; paragraph bridging p. 1718 and 1719; Fig. 1). Matsuzawa et al. teach that the size of the nanoparticles decreases with increasing gelatin concentrations (p. 1720, column 1).

Matsuzawa et al. do not teach a targeting ligand (claim 66). However, using a targeting ligand is suggested by the prior art. For example, Levy et al. teach targeting nanoparticles to specific cells by coating the nanoparticles with polypeptide which provide specific cellular uptake by binding to a cell surface receptor; coating involves freeze-drying to produce a physically-adsorbed coating (Abstract; p. 13, lines 1-9 and 18-20; p. 14, lines 3-9; p. 17, lines 1-9; p. 20, lines 16-20; p. 38, lines 4-8; p. 39, Table

1). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the microparticles of Matsuzawa et al. by coating them with a polypeptide capable of binding a cell-surface receptor, with a reasonable expectation of success. One of skill in the art would have been motivated to do so because the prior art teaches the necessity of localized therapy via sustained drug delivery to cells of interest (see Levy et al., p. 3, lines 9-15). One of skill in the art would have reasonably expected to be successful in doing such because the prior art teaches that microparticles and nanoparticles can be successfully coated with polypeptides.

Matsuzawa et al. do not teach nanoparticles having a size of 50 nm (claim 66). However, Levy et al. teach that the conditions of the solvent-evaporation technique such as the one of Iwata et al. could be manipulated to obtain nanoparticles with a size of 20-35 nm (p. 30, lines 4-12; Example 6). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the teachings of Matsuzawa et al. according to Levy et al., with a reasonable expectation of success. One of skill in the art would have been motivated to do so because Levy et al. teach that that these particles are suitable for intravascular administration since, due to their small size, they can easily penetrate the arterial wall and access target tissues (p. 97, lines 11-15).

Matsuzawa et al. and Levy et al. do not teach precipitating the polypeptide coat with a cationic precipitating agent such as Li^+ (claim 66). However, doing such is suggested by the prior art. For example, Levy et al. teach stabilizing the polypeptide coats by freeze-drying, which induces protein denaturation by precipitation (see Chang et al., Abstract). Furthermore, Li^+ was known in the prior art as a protein denaturing

agent (see Kondo et al., Abstract). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Matsuzawa et al. and Levy et al. by precipitating the protein coat with Li^+ to achieve the predictable result of producing a physically-adsorbed coating

With respect to the limitation of the bioactive agent being a polynucleotide (claim 67), it would have been obvious to one of skill in the art to use the nanoparticles in gene therapy, because the Levy et al. teach using nanoparticles in gene therapy (p. 10, lines 8-13; p. 12, lines 14-19; p. 110, lines 14-19). With respect to the limitation of a condensing agent (claims 137 and 139), it would have been obvious to one of skill in the art to use such because Levy et al. teach using DNA condensing agents such as histones and PLL to protect the polynucleotides from degradation by nucleases (p. 117, lines 6-15).

Thus, the claimed invention was *prima facie* obvious at the time it was made.

The arguments are answered below to the extent that they pertain to the instant rejection.

The applicant argues that Davies is silent on a core of bioactive component, as it is on a shell. In response, since the instant rejection is an obviousness-type rejection, Davies does not have to teach each and every claimed limitation. In fact, Davies was only cited to evidence that Span 80 has a HLB of less than 5.0.

The applicant argues that Chang describes an investigation of freezing-induced denaturation of proteins that can occur in the development of protein pharmaceuticals and result, for example, from prolonged storing in a frozen state. The invention at hand is entirely different. Chang is likely to offer little more than the desire to avoid freeze-drying polypeptide coatings based on concern regarding consequent denaturation of the polypeptide.

This is not found persuasive because the rejection is based on a combination of references and not on Chang alone. Specifically, Levy teaches stabilizing the protein shell by lyophilization (i.e., by denaturing the protein). Chang was only cited to evidence that lyophilization denatures proteins.

The arguments regarding Kondo are not found persuasive for the same reasons as set froth above.

The applicant argues that Levy teaches obtaining 20-35 nm particles by using a very specific co-solvent; however, none of the formulations actually prepared and characterized in Levy's examples has an average particle diameter of less than 50 nm. Furthermore, the ultrasmall nanoparticles do not include a shell comprising a polypeptide and Li^+.

This is not found persuasive. Levy’s example 6 specifically teaches how to obtain the 20-35 nm particles and the co-solvent system disclosed in Example 6 also applies to w/o/w emulsions (compare the co-solvent system disclosed on p. 18, lines 8-

15 for incorporation of hydrophilic agents into w/o/w emulsions with the co-solvent system disclosed in Example 6). Furthermore, Levy teaches that parameters other than the solvent system influence the size, for example the amount of energy applied with the sonicator and the concentration of the polymer (see p. 30, lines 4-10 and Example 6). Matsuzawa et al. also teach that the gelatin concentration (i.e., the polymer concentration) influences the size of the nanoparticles. Apart from an argument, the applicant did not provide any evidence that, based on the teachings in the prior art, one of skill in the art would not have been able to obtain particles smaller than 50 nm.

With respect to the argument that Levy's ultrasmall nanoparticles do not include a shell comprising a polypeptide and Li^+, it is noted that Levy does not have to teach each and very claimed limitation.

The applicant argues that one of the conditions cited by Levy to obtain ultrasmall particles is the use of DMAB, CTAB, and CTAC, all hydrophilic surfactants having HLB values of 10 or higher. Thus, Levy's "ultrasmall nanoparticles" result from the use of hydrophilic surfactants. A person of ordinary skill in the art would not be motivated by Levy to consider utilizing a surfactant with an HLB value of less than 6 to prepare nanocapsules with an average diameter of less than 50 nm.

This is not found persuasive. First, Example 6 teaches obtaining ultrasmall particles in the absence of DMAB, CTAB, and CTAC. Second and importantly, the instant rejection is based on incorporating hydrophilic agents into a first w/o emulsions and Levy's teachings of DMAB, CTAB, and CTAC do not apply to w/o emulsions. It was

common knowledge in the art that hydrophilic surfactants are not suitable to form the w/o emulsion necessary to incorporate the hydrophilic drugs. Levy teaches that only hydrophobic surfactants such as Span are suitable to form the first w/o emulsion for the incorporation of hydrophilic drugs; hydrophilic surfactants such as quaternary ammonium compounds including DMAB only form o/w emulsions, which are not suitable to incorporate hydrophilic agents (please note that CTAB and CTAC are also quaternary ammonium compounds) (see p. 17, line 16 to p. 18, line 7). Thus, Levy does not teach away from utilizing a surfactant with an HLB value of less than 6 to incorporate hydrophilic drugs into nanocapsules with an average diameter of less than 50 nm. One of skill in the art would have known to apply Levy's teachings to the w/o/w formulation of Matsuzawa et al. to further decrease the size of their nanoparticles. The applicant did not provide any evidence to the contrary.

The applicant argues that Ueda states that the W/O//W method seem not to be feasible for the preparation of nanoparticles in view of the particle size requirement." (page 594, 4th paragraph).

This is not found persuasive because Matsuzawa et al. and Levy do teach obtaining nanoparticles by using the W/O//W method.

12. Claims 66, 67, 87-89, 91-93, 133-135, 137, and 139-141 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matsuzawa et al. taken with each Davies et

al., Levy, Chang et al., and Kondo et al., in further view of Schneider et al. (FEBS Letters, 1998, 429: 269-273, of record).

The teachings of Matsuzawa et al., Davies et al., Levy et al., Chang et al., and Kondo et al. are applied as above for claims 66, 67, 87-89, 91-93, 135, 137, and 139. Matsuzawa et al., Davies et al., Levy et al., Chang et al., and Kondo et al. do not teach tenascin (claims 133, 134, 140, and 141). Schneider et al. teach identification of a polypeptide derived from the C-terminus of tenascin (claims 133 and 140) capable to bind to $\alpha_9\beta_1$ integrins on the cell surface, i.e., Schneider et al. also teach a ligand that targets a receptor for tenascin (claims 134 and 141) (Abstract, p. 272, column 2 first paragraph and Fig. 4). Schneider et al. also teach their peptide as being suitable to mediate specific gene delivery to $\alpha_9\beta_1$ integrin-expressing cells (Abstract, p. 269, column 2, second paragraph, p. 272, column 2, second and third paragraphs). It would have been obvious to one of skill in the art, at the time the invention was made to modify the nanoparticles of Matsuzawa et al., Davies et al., Levy et al., Chang et al., and Kondo et al. by coating them with tenascin with the intent to target the particles to $\alpha_9\beta_1$ integrin-expressing cells, with a reasonable expectation of success. The motivation to do so is provided by Schneider et al., who teach that using ligands for $\alpha_9\beta_1$ integrin is promising for the development of targeted gene therapy (Abstract; p. 269). One of ordinary skill in the art would have been expected to have a reasonable expectation of success in making such particles because Matsuzawa et al., Davies et al., Levy et al., Chang et al., and Kondo et al. teach that polypeptides can be successfully used to coat their nanoparticles.

Thus, the claimed invention was *prima facie* obvious at the time it was made.

The applicant argues that the previously cited later Schneider reference (1999 FEBS Letters 458:329-332) teaches that when polypeptide-DNA complexes were associated with a delivery vehicle (LipofectAMINE), targeting specificity was reduced. This led to the conclusion that "in the presence of the LipofectAMINE internalization of the complex occurs to a large extent by an integrin-independent mechanism." This leaves the person of ordinary skill in the art with an understanding that the polypeptide in question was not effective in targeted gene delivery when associated with a delivery vehicle (such as, for example, a nanocapsule according to the invention).

This is not found persuasive because it is just an argument not supported by any evidence. The applicant has no basis to extrapolate the teachings related to LipofectAMINE to any drug delivery vehicle. Furthermore, there is no teaching in Schneider that the tenascin-derived peptide is not suitable for targeted delivery in the presence of LipofectAMINE. In fact Schneider teaches that, although internalization of the complex occurs to a large extent by an integrin-independent mechanism in the presence of the LipofectAMINE, cell specificity was still significant and thus, the combination is suitable for targeted delivery *in vivo* (see Abstract; p. 331, column 1). Thus, Schneider does not teach away from using the tenascin-derived peptide for targeted delivery.

13. Claims 66, 67, 87-89, 91-94, 135, 137 and 139 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matsuzawa et al. taken with each Davies et al., Levy et al., Chang et al., and Kondo et al., in further view of Magdassi et al. (WO 98/07410).

The teachings of Matsuzawa et al., Davies et al., Levy et al., Chang et al., and Kondo et al. are applied as above for claims 66, 67, 87-89, 91-93, 135, 137, and 139. Matsuzawa et al., Davies et al., Levy et al., Chang et al., and Kondo et al. do not teach further adding a cation selected from the group recited in claims 94. Magdassi et al. teach using cations such as Ca^{2+}, Ba^{2+}, Gd^{2+}, Ni^{2+}, $Al^{2+}$and Mn^{2+} to precipitate protein shells (Abstract; p. 9, lines 25-29; claims 4 and 6). It would have been obvious to one of skill in the art, at the time the invention was made, to further add Ca^{2+}, Ba^{2+}, Gd^{2+}, Ni^{2+}, Al^{2+} or Mn^{2+} to achieve the predictable result of precipitating the protein shell. Thus, the claimed invention was *prima facie* obvious at the time it was made.

14. Claims 66, 67, 87-93, 135-137 and 139 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matsuzawa et al. taken with each Davies et al., Levy et al., Chang et al., and Kondo et al., in further view of Krishnan et al.

The teachings of Matsuzawa et al., Davies et al., Levy et al., Chang et al., and Kondo et al. are applied as above for claims 66, 67, 87-89, 91-93, 135, 137, and 139. Matsuzawa et al., Davies et al., Levy et al., Chang et al., and Kondo et al. do not teach acetylenic diols such as 2, 4, 7, 9-tetramethyl-5-decyne-4,7-diol (claims 90 and 136). However, using such is suggested by the prior art. For example, Levy et al. teach that using hydrophobic surfactants (i.e., an HLB less than 6.0, see applicant's arguments

filed on 12/22/2010) is necessary for the incorporation of hydrophilic agents (p. 17, line 16 to p. 18, line 7). Furthermore, 2, 4, 7, 9-tetramethyl-5-decyne-4,7-diol was known in the prior art as having an HLB of 3 (see Krishnan et al., Abstract, p. 357, column 2, last paragraph). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the nanoparticles of Matsuzawa et al., Davies et al., Levy et al., Chang et al., and Kondo et al. by replacing their Span 80 with any surfactant with an HLB lower than 5.0, including the well-known 2, 4, 7, 9-tetramethyl-5-decyne-4,7-diol, to achieve the predictable result of efficiently incorporating hydrophilic therapeutic agents such as nucleic acids into nanoparticles. Thus, the claimed invention was *prima facie* obvious at the time it was made.

15. Claims 66, 67, 87-89, 93, 94, 135, 136, 137, and 139 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ueda et al. taken with each Landry et al., Ghitescu et al., Kondo et al., and Boulikas, in further view of in further view of Magdassi et al.

The teachings of Ueda et al., Landry et al., Ghitescu et al., Kondo et al., and Boulikas are applied as above for claims 66, 67, 87-89, 93, 135, 137, and 139. Ueda et al., Landry et al., Ghitescu et al., Kondo et al., and Boulikas do not teach do not teach further adding a cation selected from the group recited in claims 94. Magdassi et al. teach using cations such as Ca^{2+}, Ba^{2+}, Gd^{2+}, Ni^{2+}, $Al^{2+}$and Mn^{2+} to precipitate protein shells (Abstract; p. 9, lines 25-29; claims 4 and 6). It would have been obvious to one of skill in the art, at the time the invention was made, to further add Ca^{2+}, Ba^{2+}, Gd^{2+}, Ni^{2+},

Al^{2+} or Mn^{2+} to achieve the predictable result of precipitating the protein shell. Thus, the claimed invention was *prima facie* obvious at the time it was made.

Conclusion

16. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Bazile et al. (Biomaterials, 1992, 13: 1093-1102) was cited in response to the arguments that, based on the teachings in the prior art, one of skill in the art would not have been able achieve nanoparticles having an average diameter of less than 50 nm. Specifically, the reference demonstrates that albumin-coated nanoparticles with different sizes, including 50 nm nanoparticles, can be successfully obtained.

17. No claim is allowed. No claim is free of prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILEANA POPA whose telephone number is (571)272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner’s supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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